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Abstract: Background The catecholamine reuptake inhibitors methylphenidate (MPH) and atomoxetine (ATX) are the most common treatments for attention deficit hyperactivity disorder (ADHD). This study compares the neurofunctional modulation and normalization effects of acute doses of MPH and ATX within medication-naïve ADHD boys during working memory (WM). Method A total of 20 medication-naïve ADHD boys underwent functional magnetic resonance imaging during a parametric WM n-back task three times, under a single clinical dose of either MPH, ATX or placebo in a randomized, double-blind, placebo-controlled, cross-over design. To test for normalization effects, brain activations in ADHD under each drug condition were compared with that of 20 age-matched healthy control boys. Results Relative to healthy boys, ADHD boys under placebo showed impaired performance only under high WM load together with significant underactivation in the bilateral dorsolateral prefrontal cortex (DLPFC). Both drugs normalized the performance deficits relative to controls. ATX significantly enhanced right DLPFC activation relative to MPH within patients, and significantly normalized its underactivation relative to controls. MPH, by contrast, both relative to placebo and ATX, as well as relative to controls, upregulated the left inferior frontal cortex (IFC), but only during 2-back. Both drugs enhanced fronto-temporo-striatal activation in ADHD relative to control boys and deactivated the default-mode network, which were negatively associated with the reduced DLPFC activation and performance deficits, suggesting compensation effects. Conclusions The study shows both shared and drug-specific effects. ATX upregulated and normalized right DLPFC underactivation, while MPH upregulated left IFC activation, suggesting drug-specific laterality effects on prefrontal regions mediating WM.

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Drug-specific laterality effects on frontal lobe activation of atomoxetine and methylphenidate in attention deficit hyperactivity disorder boys during working memory

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Background. The catecholamine reuptake inhibitors methylphenidate (MPH) and atomoxetine (ATX) are the most common treatments for attention deficit hyperactivity disorder (ADHD). This study compares the neurofunctional modulation and normalization effects of acute doses of MPH and ATX within medication-naïve ADHD boys during working memory (WM).

Method. A total of 20 medication-naïve ADHD boys underwent functional magnetic resonance imaging during a parametric WM n-back task three times, under a single clinical dose of either MPH, ATX or placebo in a randomized, double-blind, placebo-controlled, cross-over design. To test for normalization effects, brain activations in ADHD under each drug condition were compared with that of 20 age-matched healthy control boys.

Results. Relative to healthy boys, ADHD boys under placebo showed impaired performance only under high WM load together with significant underactivation in the bilateral dorsolateral prefrontal cortex (DLPFC). Both drugs normalized the performance deficits relative to controls. ATX significantly enhanced right DLPFC activation relative to MPH within patients, and significantly normalized its underactivation relative to controls. MPH, by contrast, both relative to placebo and ATX, as well as relative to controls, upregulated the left inferior frontal cortex (IFC), but only during 2-back. Both drugs enhanced fronto-temporo-striatal activation in ADHD relative to control boys and deactivated the default-mode network, which were negatively associated with the reduced DLPFC activation and performance deficits, suggesting compensation effects.

Conclusions. The study shows both shared and drug-specific effects. ATX upregulated and normalized right DLPFC underactivation, while MPH upregulated left IFC activation, suggesting drug-specific laterality effects on prefrontal regions mediating WM.

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Key words: Atomoxetine, attention deficit hyperactivity disorder, functional magnetic resonance imaging, methylphenidate, n-back, working memory.

Introduction

Attention deficit hyperactivity disorder (ADHD) is characterized by age-inappropriate symptoms of inattention, impulsivity and hyperactivity (APA, 2000). One of the key neuropsychological deficits is in working memory (WM) (Martinussen *et al.* 2005), defined as

the temporary storage and manipulation of information (Baddeley, 1996).

Children with ADHD have consistently shown deficits in verbal–auditory and visuo-spatial WM tasks (Rommelse *et al.* 2008; Toplak *et al.* 2008; Gau & Shang, 2010; Rhodes *et al.* 2011; for meta-analyses, see Martinussen *et al.* 2005 and Willcutt *et al.* 2005) including visual–object (Pasini *et al.* 2007) and phonological n-back tasks (Klein *et al.* 2006; Pasini *et al.* 2007; Kobel *et al.* 2009). These deficits have been shown to be underpinned by functional magnetic resonance imaging (fMRI) evidence for reduced fronto-striatal and temporo-parietal activation during visuo-spatial (Silk

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et al. 2005; Vance *et al.* 2007) and verbal WM tasks (Kobel *et al.* 2009).

The stimulant methylphenidate (MPH) and the non-stimulant atomoxetine (ATX) are the most commonly prescribed pharmacological treatments for ADHD, showing comparable efficacy in 65–70% of cases (Hazell *et al.* 2010). However, the drug-specific mechanisms of action on brain function in ADHD patients are unknown.

MPH blocks dopamine (DA) transporters in the striatum (Volkow *et al.* 1998) and norepinephrine (NE) transporters (NET) in NET-rich regions including prefrontal regions, where it enhances both catecholamines (Hannestad *et al.* 2010). ATX is a selective pre-synaptic NET blocker affecting NE and DA in the prefrontal cortex (Bymaster *et al.* 2002) and NE in the thalamus, locus coeruleus and cerebellum, with minimal striatal effects (Gallezot *et al.* 2011).

Placebo-controlled studies in medication-naïve ADHD patients showed that a single dose of MPH upregulated and/or normalized the fronto-striatal, temporoparietal and cerebellar underactivations during cognitive control tasks (Rubia *et al.* 2009a,b, 2011a,b), with similar effects being reported in previously medicated children compared with off-medication status (Vaidya *et al.* 1998; Shafritz *et al.* 2004; Epstein *et al.* 2007).

Few fMRI studies, however, have tested for MPH effects on WM in ADHD children, with inconsistent results. Thus, in previously medicated ADHD children compared with controls, MPH normalized the inferior and medial frontal cortices (IFC/MFC) and striatal underactivation during a delayed matched to sample task (Prehn-Kristensen *et al.* 2011) and upregulated activation and functional integration in fronto-parietal WM networks during a Sternberg WM task (Wong & Stevens, 2012). However, a single dose of MPH downregulated MFC and parietal activation during a delayed WM match-to-sample task in female ADHD subjects (Sheridan *et al.* 2010) or had no effects in ADHD boys (Kobel *et al.* 2009). These studies, however, did not include a placebo condition, had small sample sizes and recruited patients with a previous history of stimulant medication, shown to affect both brain activation and structure (Nakao *et al.* 2011; Hart *et al.* 2012, 2013).

In the only placebo-controlled cross-over study comparing the effects of single-dose challenges of MPH and ATX in medication-naïve children with ADHD, MPH showed drug-specific upregulation and normalization effects during motor response inhibition in the right IFC and cerebellum, while both drugs normalized left IFC underactivation (Cubillo *et al.* 2012b).

However, no fMRI study has as yet investigated the effects of ATX on brain activation in ADHD patients during WM, or compared its effects with those of

MPH. In healthy adults, acute ATX administration upregulates the IFC and superior temporal gyrus (STG) activation during inhibitory tasks (Chamberlain *et al.* 2009; Graf *et al.* 2011), and using multivariate pattern recognition analyses ATX had relatively stronger deactivation effects on the default-mode network (DMN) while MPH has relatively stronger upregulating effects on WM networks (Marquand *et al.* 2011).

We therefore conducted a randomized, double-blind, placebo-controlled, cross-over pharmacological fMRI study to test for drug-specific effects of a single clinical dose of either MPH or ATX on brain activation of medication-naïve boys with ADHD during a WM task. We chose a parametric verbal WM task, given: (a) the impact of verbal WM deficits on academic performance; (b) prior evidence for impairments in this task in ADHD children (Martinussen *et al.* 2005; Willcutt *et al.* 2005; Pasini *et al.* 2007; Kobel *et al.* 2009); and (c) evidence for more pronounced impairments in ADHD with increasing WM load (Goldberg *et al.* 2005; Kobel *et al.* 2009; Gau & Shang, 2010). The focus on single rather than long-term drug effects on neurofunctional mechanisms avoids potential confounds including side effects, symptomatic improvement or chronic effects on brain activation. We furthermore compared brain activation during the WM task in patients under each drug condition with that of age-matched healthy controls to test for potential drug normalization effects. Based on previous evidence on the n-back task, we hypothesized that ADHD patients would be more impaired with increasing WM load (Kobel *et al.* 2009). Based on previous fMRI studies of WM in ADHD children (Prehn-Kristensen *et al.* 2011), we hypothesized that ADHD boys would show underactivation relative to controls in dorsolateral prefrontal cortex (DLPFC) and parietal regions. Furthermore, based on previous findings of frontostriatal upregulation by single doses of MPH of brain activation in ADHD (Vaidya *et al.* 1998; Shafritz *et al.* 2004; Rubia *et al.* 2009a, 2011a,b; Prehn-Kristensen *et al.* 2011) and of ATX on frontal brain activation in healthy adults (Chamberlain *et al.* 2009; Graf *et al.* 2011), we hypothesized that both drugs would upregulate and normalize the reduced activation in the lateral PFC and that MPH would additionally enhance basal ganglia activation.

Method

Subjects

A total of 20 medication-naïve right-handed boys (aged 10–17 years) were recruited from clinics who had a clinical diagnosis of ADHD, inattentive/hyperactive-impulsive combined subtype, as assessed by

an experienced child psychiatrist using the standardized Maudsley diagnostic interview that assesses ADHD according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) criteria and is of standard use in the UK (Goldberg & Murray, 2002). ADHD boys scored above the clinical threshold for hyperactive-impulsive/inattentive symptoms on the Strengths and Difficulties Questionnaire for parents (SDQ; Goodman & Scott, 1999), the Conners' Parent Rating Scale (CPRS-R; Conners *et al.* 1998), and below the clinical threshold on the Social Communication Questionnaire (SCQ; Rutter *et al.* 2003) (Supplementary Table 1). Patients were scanned in a double-blind, placebo-controlled, cross-over design. On each scanning session, they received a single dose of either placebo (vitamin C: 50 mg), MPH (Equasym: 0.3 mg/kg, range 5–20 mg) or ATX (Strattera: 1 mg/kg, range 16–66 mg), in a pseudo-randomized order, and remained medication-free between scans. A Latin square design was used for the randomization to achieve counterbalanced effects. Dosages were determined following NICE guidelines of clinical efficacious dosages with minimal side effects at the time of the study (National Institute for Health and Clinical Excellence, 2008). Based on pharmacokinetic evidence, both medications were administered 1.5 h before the scan to allow for maximum absorption (Chan *et al.* 1983; Witcher *et al.* 2003). The same or similar dosages and time lapses between drug administration and scan have shown to be sufficient to observe changes in brain activation and performance in ADHD patients (MPH) (Lijffijt *et al.* 2006; Rubia *et al.* 2011a,b) and healthy controls (ATX) (Chamberlain *et al.* 2007, 2009). All three medications were over-encapsulated using the same capsules by the pharmacist.

A total of 20 right-handed healthy boys (aged 10–17 years) were recruited through advertisement in the same geographical South London area of the UK. They scored below clinical cut-offs for the SDQ, SCQ and CPRS-R. They were scanned once, unmedicated.

Exclusion criteria for all participants were an intelligence quotient (IQ) below 70 on the Wechsler Intelligence Scale for Children, 4th version (WISC-IV; Wechsler, 2004) (administered in the clinics: $n=7$) or in the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) (administered in our laboratory: $n=13$), history of substance abuse or neurological deficits, presence of psychiatric disorders (except for ADHD and conduct disorder/oppositional defiant disorder in the ADHD group: $n=2$), learning disability, and reading, speech or language disorder.

One-way analyses of variance (ANOVAs) showed no between-group differences for age ($F_{1,38}=0.88$, $p<0.35$) but did so for IQ ($F_{1,38}=42$, $p<0.001$)

(Supplementary Table 1). Low IQ is associated with ADHD (Bridgett & Walker, 2006). Although commonly conducted in case-control studies, analysis of covariance is statistically illegitimate when the covariate is an attribute of the disorder and when groups were not randomly selected (Evans & Anastasio, 1968; Miller & Chapman, 2001; Dennis *et al.* 2009). Furthermore, WM has been shown to be closely associated with IQ and is part of the WISC-IV (Wechsler, 2004). Therefore, co-varying for IQ during this task would in fact mean co-varying for any potential group differences in WM. Consequently, all analyses were conducted without IQ as a covariate. However, in order to test for potential effects of outliers, we repeated the fMRI analyses excluding subjects with an IQ more than 2 s.d. above or below average (i.e. four subjects in each group).

Participants were paid £50 for each scanning session. Parental/child informed consent/assent and approval from the local ethical committee were obtained.

WM task (*n*-back)

Subjects practised the task once before scanning. The 6-min block design WM task (Ginestet & Simmons, 2011) consists of four conditions. During '1-back', '2-back' and '3-back' conditions, subjects are presented with series of letters (A–Z) (1 s duration, inter-trial interval=2 s) and must respond with their right thumb using a button box whenever the letter presented is the same as one, two or three before it, respectively (e.g. 2-back: B/J/A/J). This requires both storage and continuous updating of stimuli being held in WM. In the baseline vigilance '0-back' condition, subjects must respond to each X that appears on the screen. The task consists of 12 randomized blocks. Before each block, written instructions of 3 s duration are shown as to which condition is next (i.e. '0-back', 1-back', etc.). In each of the WM blocks of 30 s duration only one WM condition is presented (i.e. 2-back), and contains 15 stimuli: three targets and 12 non-targets. Each condition is presented three times. Performance data were recorded during scanning. The dependent variable is accuracy (percentage of correctly identified targets).

fMRI acquisition and analyses

Gradient-echo echoplanar MR imaging (EPI) data were acquired on a GE Signa 3 T Horizon HDx system (General Electric, USA) at the Centre for Neuroimaging Sciences, Institute of Psychiatry, King's College London, UK. A semi-automated quality-control procedure ensured consistent image quality (Simmons *et al.* 1999). A quadrature birdcage head coil was used for radio frequency transmission and reception.

Table 1. Performance data for 20 healthy control boys and 20 boys with ADHD under each medication condition

Performance variable	Task condition	Controls	ADHD placebo	ADHD MPH	ADHD ATX
Accuracy (% correct responses)	0-back	96 (11)	98 (4)	99 (3)	97 (8)
	1-back	92 (17)	97 (6)	98 (6)	95 (16)
	2-back	87 (22)	77 (26)	82 (25)	81 (26)
	3-back	68 (21)	60 (28)	66 (24)	63 (27)

ADHD, Attention deficit hyperactivity disorder; MPH, methylphenidate; ATX, atomoxetine.

In each of 39 non-contiguous planes parallel to the anterior–posterior commissure line, 186 T₂*-weighted MR images depicting blood oxygen level-dependent (BOLD) contrasts covering the whole brain were acquired (echo time=30 ms, repetition time=2 s, flip angle=75°, in-plane resolution=3 mm, slice thickness=3.5 mm, slice-skip=0.5 mm). This EPI dataset provided complete brain coverage.

Blocked fMRI data were acquired in randomized block presentation, and analysed using the non-parametric XBAM software (Brammer *et al.* 1997; Bullmore *et al.* 1999, 2001; Brain Image Analysis Unit, 2011). Methods for individual fMRI analyses and group mapping are described in the Supplementary text. For between-group comparisons, a 2×3 split plot-design ANOVA (groups: controls, patients; WM load: 1-back, 2-back, 3-back, each separately contrasted with 0-back) was conducted. For within-group comparisons, a 3×3 factorial-design repeated-measures ANOVA (drug condition: placebo, MPH, ATX; WM load: 1-back, 2-back, 3-back, separately contrasted with 0-back) was conducted. Statistical measures of BOLD response were extracted for each participant in each of the clusters of activation differences for each of the three contrasts, and *post hoc* analyses were conducted to clarify the direction of the differences. Within patients, repeated-measures ANOVAs on the extracted BOLD response measures were conducted to test for potential order effects.

Performance analysis

For the main performance measure of accuracy within patients, repeated-measures ANOVAs were conducted with drug condition (placebo, MPH, ATX) and WM load (0-back, 1-back, 2-back, 3-back) as within-subject factors. For case-control comparisons, three repeated-measures ANOVAs (controls *versus* ADHD under placebo; controls *versus* ADHD under MPH and controls *versus* ADHD under ATX) were conducted with WM load as the within-subjects factor and group as the between-subjects factor. Repeated-measures ANOVAs were used to test for potential scan order effects.

Results

Performance data

Across all participants, there was a significant WM load effect in accuracy ($F_{3,114}=49$, $p<0.001$), showing that accuracy decreased with increasing WM load (Table 1).

In case-control comparisons, no group effects were found. However, as hypothesized, there was a significant interaction effect between WM load and group in accuracy when healthy controls were compared with patients under placebo ($F_{3,114}=3$, $p<0.035$) due to patients being more accurate during 0-back and 1-back but less accurate during 2- and 3-back than healthy controls (Table 1).

Within patients, no effects of drug condition or WM load×drug condition were detected on performance variables.

No other group, group×WM load interaction or drug order effects were observed.

Brain activation

Motion

Participants were excluded if they had >3 mm in the X or Y dimensions. Multivariate ANOVA showed no significant group differences between controls and ADHD patients under each drug condition in the extent of mean rotation and translation movement parameters in the three-dimensional Euclidean space ($F_{6,152}=1$, $p=0.43$).

Within-group brain activations

Within-group brain activations are shown in Supplementary Fig. 1 and described in the Supplementary text and Supplementary Table 2.

ANOVA between-group comparisons between healthy controls and ADHD boys under placebo, MPH or ATX

Placebo

Controls compared with patients under placebo showed enhanced activation in the bilateral DLPFC

(Table 2, Fig. 1a). There was no enhanced activation in patients compared with healthy controls.

Given that patients were less accurate than controls in the 2- and 3-back conditions, we hypothesized that accuracy would be positively correlated with DLPFC activation in these conditions. Hence, one-tailed Pearson correlations were conducted in both groups separately between statistical measures of the BOLD response in the left and right DLPFC and a composite score of their accuracy during 2- and 3-back. At a trend level, activation in the right DLPFC was correlated positively with accuracy within controls ($r=0.35$, $p<0.06$). No correlations were observed for left DLPFC activation.

MPH

After the single dose of MPH, patients compared with controls showed underactivation in the same left and right DLPFC clusters as under placebo. However, ADHD patients relative to controls showed additional, enhanced activation in a cluster comprising the right STG/premotor cortex, striatum/thalamus, insula, reaching into the cerebellar vermis (Table 2, Fig. 1a). To test whether the increased right medial fronto-STG-striatal activation in patients under MPH was compensatory for the reduced bilateral DLPFC activation, statistical measures of BOLD response were extracted for each patient in these three clusters and correlated with the DLPFC activation clusters as well as with the accuracy composite score. Pearson correlations showed that the medial fronto-STG-striatal activation was negatively correlated with the left DLPFC activation ($r=-0.5$, $p<0.012$) and positively with accuracy ($r=0.37$, $p<0.05$).

ATX

Under the single dose of ATX, patients compared with controls still showed reduced activation in the left DLPFC. However, they no longer showed underactivation of the right DLPFC. In addition, abnormally enhanced activation was observed in ADHD relative to controls in a right-lateralized cluster of IFC and STG, insula, thalamus and striatum (Table 2, Fig. 1a), which within patients was positively correlated with accuracy ($r=0.54$, $p<0.007$).

Repeated-measures ANOVA within patients, for all three contrasts, showed no significant scan order effects on the extracted BOLD response measures.

When those subjects whose IQ scores were more than 2 s.d. above or below average were excluded, all findings remained, although at a more lenient p value ($p<0.03$).

Effect size comparisons of case-control conditions to test for significant 'normalization' effects

To establish whether the group differences between controls and patients under each drug condition were significantly different, we directly compared the effect sizes (ES) of the group differences from the three case-control comparisons (Matthews & Altman, 1996) (see details in the Supplementary text).

In the right DLPFC, the ES of the case-control contrast under ATX was significantly different from the ES of the case-control comparison under MPH ($p<0.03$), suggesting that ATX significantly enhanced activation in this region relative to MPH. For the cluster of enhanced right fronto-STG-striatum activation under MPH relative to controls the ES of the case-control contrast under MPH was significantly higher than the ES of the case-control comparisons under placebo ($p<0.004$) and ATX ($p<0.05$). Finally, for the cluster of enhanced right IFC-STG-striato-thalamic activation under ATX relative to controls, the ES was significantly larger for the case-control contrast under ATX relative to those of the case-control comparisons under placebo ($p<0.007$) and under MPH ($p<0.03$) (Supplementary Table 3).

ANOVA within-patient comparison between placebo, MPH and ATX

Given the reduced activation in the left and right DLPFC, we tested for significant upregulation effects of both drugs in the frontal cortex. The Talairach Client (Lancaster *et al.* 1997, 2000) was used to define a mask of the frontal lobe, restricting the analysis to those voxels present in the mask. A significant effect of drug condition was observed in a cluster in the right DLPFC [13 voxels, peak Talairach coordinates (x , y , z): 25, 44, 26; Brodmann area (BA) 10/9, $p<0.044$], which was due to significantly enhanced activation when under ATX relative to MPH ($p<0.002$), as well as when under placebo relative to MPH ($p<0.01$) (Fig. 1b). There were no significant correlations between brain activation changes and performance.

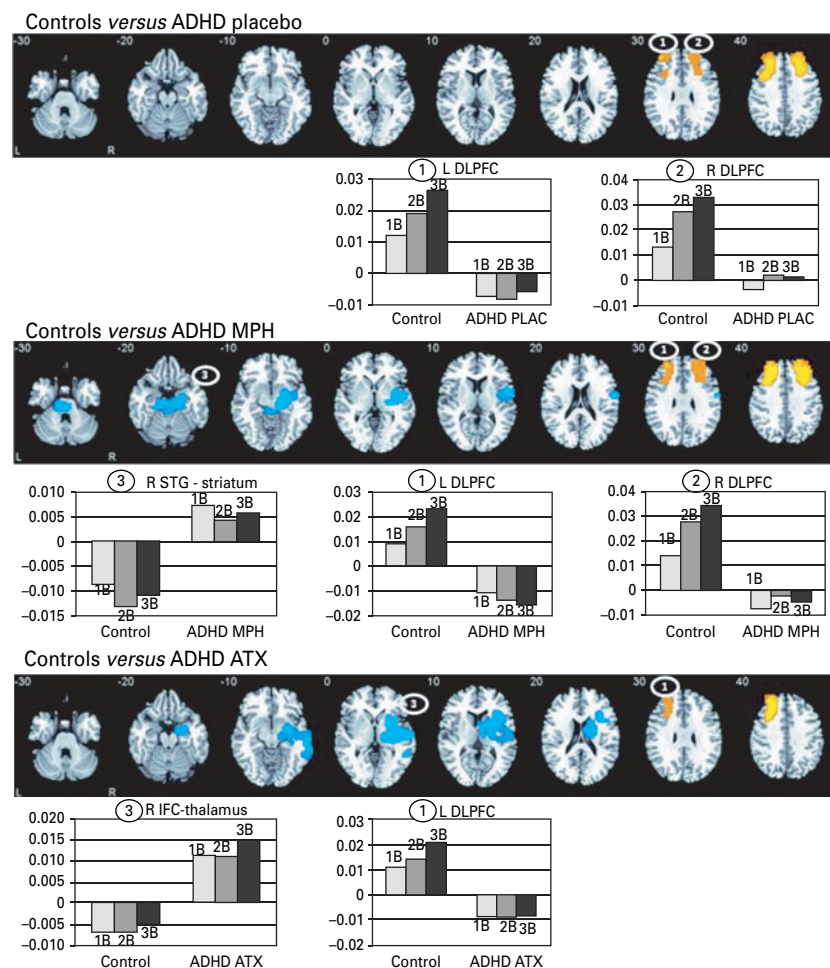
Interaction effects

Between-groups comparisons: WM load \times group

No significant interaction effects were observed in the comparison between healthy controls and patients under placebo.

In the comparison between healthy and ADHD boys under MPH, a significant interaction of group \times WM load was observed in the left IFC reaching into the DLPFC, putamen and anterior insula, due to enhanced activation in ADHD under MPH relative to controls during 2-back ($p<0.01$). Additional interaction effects

(a)



(b)

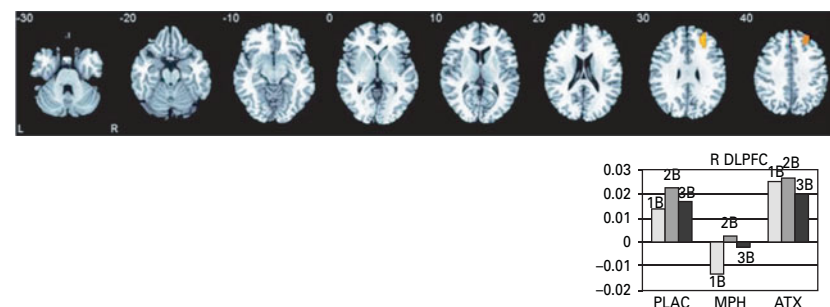


Fig. 1. Results from the main group comparisons and the within-patient drug condition analysis. (a) Between-group analysis of variance (ANOVA) comparisons between healthy control boys and boys with attention deficit hyperactivity disorder (ADHD) under either placebo (PLAC), methylphenidate (MPH) or atomoxetine (ATX) (main effect of group differences): axial sections showing the ANOVA between-group differences in brain activation between healthy control boys and boys with ADHD under each drug condition (placebo, MPH, ATX). For ease of view, clusters and their correspondent bar chart are numbered. Clusters in orange denote areas where control boys showed enhanced activation compared with ADHD boys, clusters in blue denote areas where ADHD boys showed enhanced activation compared with control boys. The graphs show the statistical measure of blood oxygen level-dependent (BOLD) (brain activation) response in each area for each group and working memory (WM) condition. The x-axis of the graphs corresponds to the statistical measure of the BOLD response in this region. In the bar charts, the labels 1B, 2B and 3B denote the BOLD response of each group in the contrasts 1-back *v.* 0-back, 2-back *v.* 0-back and 3-back *v.* 0-back, respectively. (b) Within-patients ANOVA comparison (main effect of drug condition). Axial sections showing the repeated-measures ANOVA results of drug condition within ADHD boys. The graphs

were observed in bilateral occipital regions extending to the cuneus, due to the enhanced deactivation of this cluster in patients under MPH compared with controls during 2-back ($p < 0.001$) (Fig. 2a, Table 3).

In the comparison between controls and patients under ATX, significant interaction effects were observed in the anterior and posterior cingulate extending to the precuneus, due to significantly enhanced activation within patients relative to controls during 1-back ($p < 0.004$) and enhanced deactivation during 3-back ($p < 0.005$) (Fig. 2a, Table 3).

Within-subjects comparison: WM load \times drug condition

Significant interaction effects were observed in the left IFC [14 voxels, peak Talairach coordinates (x, y, z): -36, 22, 9; BA 44/45, $p < 0.019$ ($p < 0.04$ Bonferroni corrected)] (Fig. 2b), due to significantly enhanced activation in this cluster during 2-back when under MPH compared with placebo ($p < 0.001$) and ATX ($p < 0.015$).

Repeated-measures ANOVAs showed no scan order effect on the extracted BOLD response measures.

Discussion

The present fMRI comparison between single-dose challenges of MPH and ATX on neural correlates of WM in children with ADHD shows both shared as well as drug-specific laterality effects on frontal activations. In line with previous studies, medication-naïve ADHD boys under placebo relative to controls showed impaired performance under high but not low WM load. This was accompanied by placebo-associated underactivation in the left and right DLPFC relative to controls. Both drugs had no effect on within-subject performance, but normalized the case-control performance deficits in the more difficult 2- and 3-back conditions in ADHD patients relative to controls, which were no longer observed under either drug. ATX had drug-specific modulation effects on the right DLPFC, which was upregulated in ADHD patients relative to MPH and significantly normalized in its underactivation relative to controls. By contrast, MPH showed a drug-specific WM load-dependent effect on the left-lateralized IFC, which was upregulated

during 2-back, both relative to controls (case-control comparison), and relative to ATX and placebo (within-subject contrast). Both drugs, in addition, elicited abnormally enhanced activation in patients relative to controls in different fronto-STG-striatal networks, which were associated with improved performance, suggesting compensatory effects. The findings therefore show both drug-specific laterality effects in the upregulation of prefrontal WM regions as well as shared effects of recruiting compensatory brain areas.

ADHD patients under placebo relative to controls showed no deficits during the first easy WM task condition. However, they were less accurate than controls during the 2-back and 3-back conditions, in line with prior evidence for more pronounced deficits in ADHD patients with increased task difficulty during verbal n-back (Kobel *et al.* 2009) and visuo-spatial WM tasks (Goldberg *et al.* 2005; Gau & Shang, 2010). Although neither drug improved performance within patients, the case-control analyses showed that both drugs normalized the between-group accuracy deficits in the 2- and 3-back condition, as they were no longer observed. The findings are in line with evidence that MPH normalizes the performance deficits shown by ADHD patients relative to controls in a verbal n-back (Kobel *et al.* 2009). The normalization effects suggest relatively small accuracy improvements that were probably underpowered to emerge in the within-subject analyses.

Compared with controls, patients showed underactivation in the bilateral DLPFC, a key region for WM, involved in the storage and coding of the temporal sequence of stimuli (Owen *et al.* 2005). The findings extend previous evidence of underfunctioning of the DLPFC in adult ADHD during WM (Valera *et al.* 2010) and in ADHD children during other attention and executive function tasks (Rubia, 2011; Cubillo *et al.* 2012a, Hart *et al.* 2012; Christakou *et al.* 2013).

The most interesting findings are those of drug-specific lateralization effects on frontal activations. While ATX showed a drug-specific right-hemispheric DLPFC upregulation and normalization effect relative to MPH, MPH showed a drug-specific left-lateralized WM load-dependent upregulation effect on left IFC/DLPFC activation during the 2-back condition relative to ATX within patients and relative to controls.

show the statistical measure of BOLD response in the cluster for drug condition and WM load condition. The x-axis of the graphs corresponds to the statistical measure of the BOLD response in this region. In the bar charts, the labels 1B, 2B and 3B denote the BOLD response of each group in the contrasts 1-back *v.* 0-back, 2-back *v.* 0-back and 3-back *v.* 0-back, respectively. Talairach z-coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the image corresponds to the right side of the brain. The maps are thresholded to give less than one type I error three-dimensional cluster per map ($p < 0.01$). L, Left; DLPFC, dorsolateral prefrontal cortex; R, right; STG, superior temporal gyrus; IFC, inferior frontal cortex.

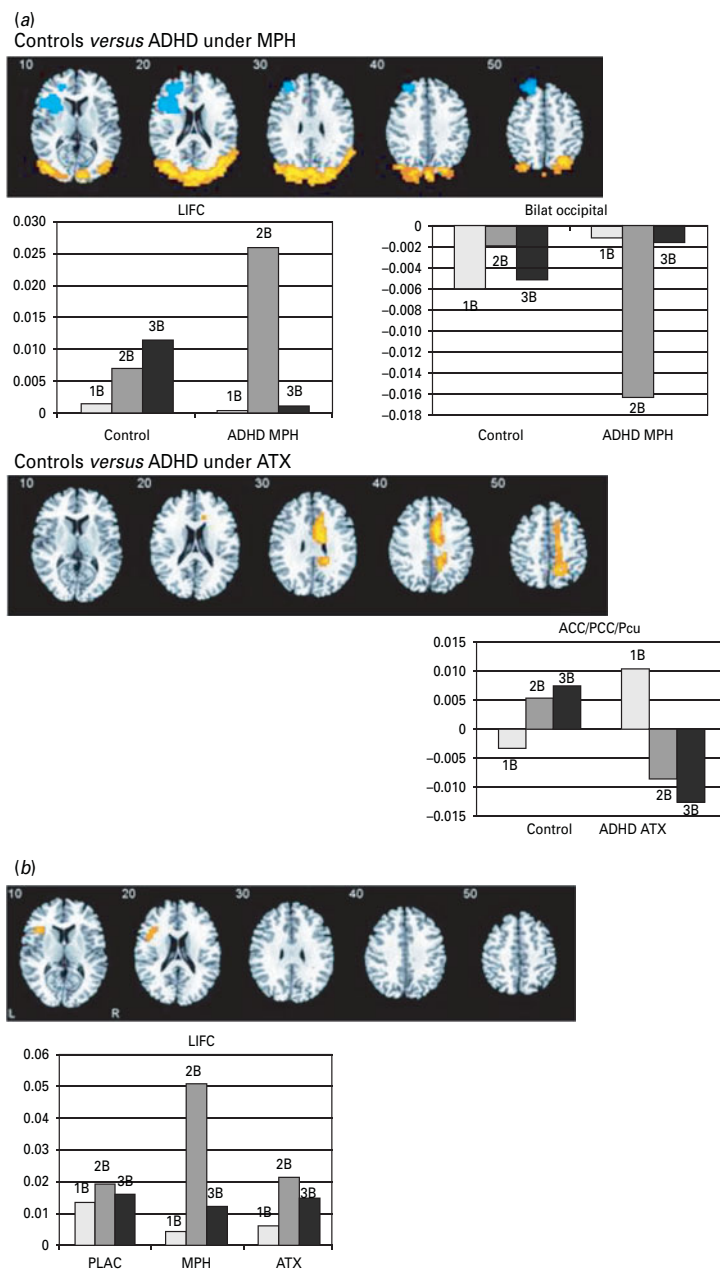


Fig. 2. Interaction effects with working memory (WM) load. (a) Axial sections showing the interaction effects between WM load and group for the between-group comparisons between healthy controls and boys with attention deficit hyperactivity disorder (ADHD) under methylphenidate (MPH), and between healthy controls and ADHD boys under atomoxetine (ATX). The graphs show the blood oxygen level-dependent (BOLD) response in each area for each group and WM load condition. In the bar charts, the labels 1B, 2B and 3B denote the BOLD response of each group in the contrasts 1-back *v.* 0-back, 2-back *v.* 0-back and 3-back *v.* 0-back, respectively. Clusters in orange denote areas where control boys showed enhanced activation compared with ADHD boys, clusters in blue denote areas where ADHD boys showed enhanced activation compared with control boys. (b) Axial section showing the interaction effects of WM load and drug condition for the within-ADHD ANOVA. The graph shows the BOLD response in each area for each drug condition during each WM load condition. In the bar charts, the labels 1B, 2B and 3B denote the BOLD response of each group in the contrasts 1-back *v.* 0-back, 2-back *v.* 0-back and 3-back *v.* 0-back, respectively. Talairach z-coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the image corresponds to the right side of the brain. The maps are thresholded to give less than one type I error three-dimensional cluster per map ($p < 0.01$). L, Left; IFC, inferior frontal cortex; Bilat, bilateral; ACC/PCC/Pcu, anterior cingulate/posterior cingulate cortex/precuneus; PLAC, placebo.

Table 2. Group differences in brain activation for between-group ANOVA comparisons between controls and boys with ADHD under either the placebo, MPH or ATX condition^a

Subject contrast	Brain regions of activation	Brodmann area	Peak Talairach coordinates: x, y, z	Voxel number	Cluster <i>p</i> value (corrected)	Cohen's <i>d</i>
Control>ADHD placebo	Right medial/superior frontal	9/8	25, 37, 31	129	0.01 (0.02)	1.28
	Left medial/superior/inferior frontal	9/8	-25, 44, 31	129	0.008 (0.016)	1.51
Control>ADHD MPH	Right medial/superior frontal	9/8	25, 44, 31	201	0.001 (0.002)	1.90
	Left medial/superior frontal	9/8	-25, 44, 31	143	0.002 (0.004)	1.73
ADHD MPH>control	Right superior temporal/parahippocampal gyri/premotor cortex/basal ganglia/thalamus/insula/amygdala/vermis cerebellum	36/22/6	18, -15, -24	297	0.005 (0.01)	1.60
Control>ADHD ATX	Left medial/superior frontal	9/8	-25, 41, 37	169	0.004 (0.008)	1.65
ADHD ATX>control	Right inferior frontal/insula/medial/superior temporal/amygdala/basal ganglia/thalamus	44/45/21/22	29, -15, -7	395	0.003 (0.006)	1.82

ANOVA, Analysis of variance; ADHD, attention deficit hyperactivity disorder; MPH, methylphenidate; ATX, atomoxetine.

^a The maps are thresholded to give less than one type I error three-dimensional cluster per map.

Table 3. Group \times WM load interaction effects on brain activation for between-group ANOVA comparisons between controls and boys with ADHD under either the placebo, methylphenidate or atomoxetine condition^a

Subject contrast	Brain regions of activation	Brodmann area	Peak Talairach coordinates: x, y, z	Voxel number	Cluster <i>p</i> value (corrected)	Cohen's <i>d</i>
ADHD MPH>control	Left inferior/middle/superior frontal/putamen	44/45/10/46/9	-36, 22, 4	237	0.007 (0.014)	0.85
Control>ADHD MPH	Right and left medial occipital/cuneus/middle temporal gyri	17/18/19/39	-25, -85, 20	546	0.001 (0.002)	1.18
Control>ADHD ATX	Right anterior/posterior cingulate gyri/precuneus	24/32/23/31/7	11, 15, 26	167	0.004 (0.008)	0.98

WM, Working memory; ANOVA, analysis of variance; ADHD, attention deficit hyperactivity disorder; MPH, methylphenidate; ATX, atomoxetine.

^a The maps are thresholded to give less than one type I error three-dimensional cluster per map.

The findings suggest potential differences in their effects on underlying catecholaminergic systems. WM is mediated in the DLPFC by noradrenergic α_2 receptors that increase neural 'signalling' (increased firing to relevant stimuli) and by dopaminergic D₁ receptors that decrease 'noise' (suppressing firing to irrelevant stimuli) (Gamo *et al.* 2010). Although ATX affects both DA and NE in the PFC (Bymaster *et al.* 2002), in non-human primates it increases 'signalling' more frequently than it decreases 'noise' (Gamo *et al.* 2010). This study thus shows for the first time that upregulation of right frontolateral activation is not only observed with a single dose of ATX in healthy adults

(Chamberlain *et al.* 2009; Graf *et al.* 2011), but also in children with ADHD, implying similar mechanisms of action in both healthy subjects and ADHD patients. Most importantly, however, we show that, during WM, the right frontal normalization and upregulation effects with ATX are drug-specific relative to MPH.

Interestingly, the finding of left IFC upregulation under the 2-back with MPH reflects the association between dopaminergic striatal function and left IFC activation during WM maintenance (Landau *et al.* 2009), in line with previous findings of predominantly left-hemispheric upregulation and normalization effects (Epstein *et al.* 2007; Rubia *et al.* 2009a, 2011b).

Therefore, the findings could possibly suggest stronger effects of ATX on predominantly right-lateralized NE-mediated WM and attention networks (Tucker & Williamson, 1984), while MPH showed stronger effects on predominantly left-lateralized fronto-striatal DA systems (Glick *et al.* 1982; Flor-Henry, 1986).

The enhanced deactivation with both drugs in regions of the DMN in ADHD relative to controls during the high WM load conditions suggest that catecholamine reuptake inhibitors not only increase task-positive but also switch off task-negative DMN activation. The findings extend prior evidence of enhanced DMN deactivation with MPH during motor inhibition in previously medicated patients relative to an off-medication condition (Liddle *et al.* 2010) to medication-naïve patients in a placebo-controlled design for another task and furthermore show for the first time that this effect is shared by ATX.

Both drugs showed abnormally enhanced fronto-STG-striatal activation in ADHD boys relative to controls, although in somewhat different locations, affecting the premotor cortex with MPH and the right IFC with ATX. The findings echo previous findings of fronto-temporo-striatal upregulation/normalization in ADHD children with MPH during WM (Pohn-Kristensen *et al.* 2011) and other cognitive control tasks (Vaidya *et al.* 1998; Epstein *et al.* 2007; Rubia *et al.* 2011a,b) and extend for the first time previous evidence of enhanced IFC/STG activation after a single-dose ATX challenge in healthy adults (Chamberlain *et al.* 2009) to a paediatric ADHD group.

The strength of the study is the double-blind, placebo-controlled design and the recruitment of medication-naïve children with ADHD, which avoids the confound of a previous history of stimulant medication (Nakao *et al.* 2011; Hart *et al.* 2012).

A limitation is the fact that groups differed in IQ. However, the findings survived when outliers were excluded from the analyses.

An important caveat is that while MPH has an immediate effect on ADHD symptoms (Greenhill *et al.* 2001), ATX reaches its maximum clinical efficacy after 12 weeks of treatment (Montoya *et al.* 2009). Given the differences of the two drugs in temporal courses to clinical efficacy, however, future studies should also compare their long-term effects on brain activation when they have reached maximum clinical efficacy. Also, while a within-group design was crucial to assess differential drug effects, it has the disadvantage that only one group was medication-naïve in the second drug and none in the third drug condition. However, the 7 days' break between scans should have minimized carry-over effects. MPH has a 3.9 h half-life (Modi *et al.* 2000). For ATX, the plasma half-life is 3 h for fast metabolizers and 16–25 h for poor

metabolizers (single dose and steady state) (Sauer *et al.* 2003; Witcher *et al.* 2003) and hence effects should have been washed out after 1 week. While we used the smallest clinical dosages with minimal side effects at the time of the study as recommended by the NICE guidelines (National Institute for Health and Clinical Excellence, 2008), some children with ADHD receive higher dosages in clinical practice, which could lead to more pronounced effects and long-term changes in catecholaminergic systems. A further limitation is that ADHD boys performed the task three times, while, for financial and ethical reasons, controls were scanned only once, unmedicated. However, the counterbalanced randomized design for the ADHD group adequately controlled for practice effects in patients, and we found no order effects for the within or the case-control studies, which suggests that these were unlikely to have confounded the between-groups analyses. Also, we included a relatively large age range. While this does not affect the within-subject analyses and controls were age-matched, a smaller age range may have resulted in less variance and more refined changes particular to specific ages, given developmental changes between late childhood and adolescence during WM and other executive functions (Crone *et al.* 2006; Bunge & Wright, 2007; Rubia, 2012). Furthermore, due to the higher prevalence of ADHD in boys (Merikangas *et al.* 2010), we only tested male adolescents, which limits the generalizability of the findings.

In conclusion, the findings show both drug-specific as well as shared effects on task-positive and task-negative WM networks. ATX appears to have a drug-specific effect of upregulating and normalizing WM-related right DLPFC dysfunction in ADHD, while MPH appears to upregulate compensatory activation of left IFC activation, but only during the 2-back condition.

Supplementary material

For supplementary material accompanying this paper visit <http://dx.doi.org/10.1017/S0033291713000676>

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Declaration of Interest

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